Support for an oligoribonucleotide consisting of a double stranded structure of 15 to 49 base pairs as claimed in claim 222 is found in the specification on page 4, lines 1-3, which states "In a further aspect the dsRNA has 10 to 1000, preferably 15 to 49 , base pairs" in combination with the open language of originally filed claims 1 and 5, which recite in part as follows; Claim 1. " ...an oligoribonucleotide with double stranded structure (dsRNA).....", and Claim 5. "Method according to one of the preceding claims wherein the dsRNA has 10 to 1000, preferably 15 to 49, base pairs..".

Support for an oligoribonucleotide that specifically inhibits the expression of said target gene, encompassed by all the pending claims, is found on page 7, lines 5-10 and 22-29, which discloses "The dsRNA can be complementary to the primary or processed RNA transcript of the target gene" and "at least one oligoribonucleotide with double stranded structure (dsRNA) for inhibiting the expression of a given target gene, where one strand of the dsRNA has a region I where at least segments are complementary to the target gene", in the exemplification in Example 2 of such inhibitory dsRNAs.

Support for an isolated mammalian cell comprising an exogenous oligoribonucleotide and an exogenous oligoribonucleotide that is vector encoded, is found in the specification on page 4, lines 5-11, which disclose that "Such dsRNA or a vector provided for coding the same can be produced synthetically or enzymatically by customary methods", and on page 6, lines 34-37 which discloses that "The above mentioned features considerably facilitate the introduction of the dsRNA or of the vector into the cell", and on page 7, lines 7-8 which discloses that "The cell can be a vertebrate cell or a human cell". Example 1 and 2 of the specification exemplifies an isolated mammalian cell comprising an exogenous oligoribonucleotide and exogenous oligoribonucleotide that is vector encoded.

Support for a structure which is fully complementary to an RNA transcript of a mammalian target gene, is found in the Examples of the instant specification, wherein the region of complementarity of each exemplified oligoribonucleotide is fully complementary to the targeted RNA transcript.

Support for the negative limitation that the oligoribonucleotide does not comprise a full length RNA transcript of a mammalian target gene goes to the heart of the invention, that is, as supported by the disclosure on page 8, lines 7-15, "Surprisingly, it has emerged that an effective inhibition of the expression of the target gene can be achieved even when the complementary region I is not more than 49 base pairs in length", and by the specification in general. The exemplifications of the claimed oligoribonucleotides in the specification clearly demonstrate duplex structures which contain two RNA strands, neither of which can be the full length target RNA transcript.

Interview

Applicant thanks Examiners Whitehead and Lacourciere for participating in a telephone interview on August 20, 2003, in which the Examiners provided a clear explanation of the rejections of record and helpful suggestions regarding claim language.

Priority

The Patent Office states that applicant has not filed a certified copy of each of the foreign priority documents (DE 19903713.2 and DE 19956568.6) as required by U.S.C. 119(b). Applicant respectively submits that certified copies of the priority documents should have been communicated from the International Bureau (PCT Rule 17.2(a)) since the instant application is a 371 application. However, in order to expedite prosecution, Applicant has attached certified copies of said priority documents, please see Exhibits A and B.

Objection to the Claims

The Office Action states that Claims 241-242 and 244 are free of the prior art, but are objected to as being dependent upon a rejected base claim (claim 221). Applicant has amended the base claim to place it in condition for allowance, as discussed below, thereby obviating this objection.

Claim Rejections – 35 U.S.C. § 112

Claims 232-238, 245 and 247 were rejected 35 U.S.C. § 112 first paragraph because the Patent Office contends that while the specification is enabled for an isolated mammalian cell comprising an exogenous oligoribonucleotide, wherein the oligoribonucleotide has a double stranded structure (dsRNA) comprising two separate RNA strands, wherein the dsRNA comprises a 3' overhang, and wherein one strand of the dsRNA has a region which is complementary to an RNA transcript of at least a part of a target gene, it does not reasonably provide enablement for any mammalian cell comprising the exogenous oligoribonucleotide. The Patent Office contends that it would require undue experimentation to extend the guidance provided by the specification regarding the delivery of dsRNA into cells *in vitro* versus into mammalian cells *in vivo,* in view of the alleged art-recognized unpredictability of specific delivery of a dsRNA in any mammalian cell.

While not acquiescing to the correctness of the Patent Office's position, and solely for the purpose of advancing prosecution, Applicant has narrowed the scope of the instant claims by amending independent claim 232 to recite "An isolated cell...". By virtue of this amendment, Applicant respectively submits that the rejection should be withdrawn.

Claim Rejections – 35 U.S.C. § 102

Applicant gratefully acknowledged the withdrawal of the 102(e) rejection of claims 221, 222, 224 and 243 as being anticipated by Shimkets et al. (U.S. Patent No. 6,486,299).

Applicant also gratefully acknowledged the withdrawal of the 102(e) rejection of claims 221, 222, 223, 232, 233, 234, 235, 236 and 243 as being anticipated by Fire et al. (U.S. Patent No. 6,506,559).

Claims 221, 223 and 224 were rejected under 102(b) as being anticipated by Alfonzo et al. (Nucleic Acid Research, Vol. 25, 3751-3759, 1997).

The Office Action states that Applicant's arguments with respect to claims 221 and 223 were considered but are moot in view of the new grounds of rejection. The Office Action also states that Alfonzo et al. teaches a double stranded RNA (dsRNA), wherein one strand has a region which is complementary to an RNA transcript of a mammalian gene, that the dsRNA

comprises a 3' overhang, wherein the RNA strands are linked together, and refers one to page 3755.

Applicant traverses the rejection on the grounds that Alfonzo et al. does not teach an oligoribonucleotide which contains each and every limitation recited by the instant claims.

First, Applicant notes that the structure of the in vivo duplex taught by Alfonzo et al. is ambiguous as to the overall length of the duplexes. Alfonzo et al. teach an in vivo model of RNA editing (splicing) in non mammalian species, i.e. kinetoplastid protozoa. The RNA editing model includes a "guide" RNA which has a region complementary to an mRNA target encoded by trypanosomatid species, (see page 3751, column 2). The "guide" mRNA itself is not a double-stranded RNA structure, but is a single stranded RNA. The guide RNA is proposed by Alfonzo et al. as a first strand to form in vivo a duplex structure with a target mRNA. Applicant notes that Alfonzo et al. does not teach an actual oligoribonucleotide itself, but only teaches schematic models of duplexes which are incorporated into at least two models of RNA editing. In the referenced Figure 2, entitled "Diagram of Models for U insertion/deletion RNA editing", the overall length of the duplex structure is not taught, nor is the length of the region of complementarity. An oligoribonucleotide having a double stranded structure, wherein the structure is not more than 49 nucleotides in length, as recited in claims 221, 223 and 224 is not taught. Therefore, Alfonzo et al. cannot anticipate the oligoribonucleotides claimed in claims 221, 223 and 224.

Second, claims 221 and 223 are clearly distinct from Alfonzo et al. and any other related art, due to the recited limitation that the oligoribonucleotide does not comprise a full length transcript as one strand of the dsRNA. Also, the oligoribonucleotide taught by Alfonzo et al. does not comprises a double-stranded structure which is complementary to an RNA transcript of a mammalian target gene" as required by claims 221, 223 and 224. The oligoribonucleotides taught by Alfonzo et al. have a dsRNA structure composed of a trypanosome encoded guide RNA and the mRNA target transcript itself. The target mRNA of the double stranded structure taught by Alfonzo et al. is from a trypanosomatid species and therefore, the dsRNA taught by Alfonzo et al. cannot specifically inhibit the expression of a mammalian target gene.

Thus, Alfonzo et al. does not meet each and every claim limitation of independent claims 221, 224, 232 and 237, and dependent claim 223, by virtue of its not teaching: (a) an oligoribonucleotide comprising a double stranded structure of a defined length, (b) of having a dsRNA region which is complementary to an RNA transcript of a mammalian target gene, and (c) of specifically inhibiting the expression of a mammalian target gene. Further, Alfonzo et al. does not anticipate independent claims 232 and 237 because it does not teach a mammalian cell comprising an exogenous oligoribonucleotide.

Applicant noted above that Alfonzo et al. teaches that the guide RNAs form anchor duplexes with mRNA by base pairing, (see column 2 of page 3751), and that the specific length of the region of complementarity is not taught. Applicant acknowledges the Examiners' comment made in the interview described above, that a string of only a few nucleotides of said guide RNA—mRNA dsRNA might be considered to be complementary to a mammalian gene.

In order to more clearly claim Applicant's invention, Applicant has amended the claims to recite that the claimed oligoribonucleotide "specifically inhibits" the expression of the mammalian target gene. Because a region of complementarity of only a few bases in a trypanosome mRNA would not be sufficient to specifically inhibit the expression of the mammalian target gene, the oligoribonucleotide taught by Alfonzo does not meet the limitation that the claimed oligoribonucleotide "specifically inhibit" the expression of the mammalian target gene. Therefore, Alfonzo et al. cannot anticipate the instant claims.

Because Alfonzo et al. does not teach each of the recited claim limitations, either explicitly or inherently, Applicant respectively requests reconsideration and withdrawal of the rejection.

Claims 221, 222, 223, 224, 225, 232, 233, 234, 235, 236, 237, 238, 239, 243 and 245 were rejected under 102(e) as being anticipated by Kmiec et al. (U.S. Patent No. 6,537,046).

Applicant traverses the rejection on the grounds that the recombinagenic oligonucleobase taught by Kmiec et al. is not identical to the oligoribonucleotide of the instant invention. In fact, the polymer taught by Kmiec et al. must be a self complementary single stranded hairpin

structure, which must contain at least one mismatch base within the self-complementary region, as is shown clearly below.

Applicant notes that Kmiec et al. teaches a nucleic acid that may be composed of either RNA or DNA. Specifically, Kmiec et al. discloses that "one or both strands of the duplex mutational vector (DMV) can optionally contain ribo-type nucleobases. In a preferred embodiment a first strand of the DMV consists of ribo-type nucleobases only while the second strand consists of deoxyribo-type nucleobases." (Column 8, lines 47-51).

However, Applicant notes that Kmiec et al. discloses that the nucleic acid must be one continuous strand forming a hairpin, and can not be two separate strands. Kmiec et al. discloses that "The DMV [duplex mutational vector] is a single oligonucleobase compound (polymer) of between 24 and 150 nucleobases. Accordingly the DMV contains a single 3' end and a single 5' end."(Column 9, lines 20-22) and also discloses that "A oligonucleobase compound has a single 5' and 3' end nucleobase, which are the ultimate nucleobases of the polymer." (Column 7, lines 32-34).

In contrast, the recitation of the double stranded structure of the oligoribonucleotide of claims 221-223, 232-236, 239, 241-245 and 247-248, requires that it comprise two separate RNA strands, and as such is distinct from the single oligonucleobase compound (polymer) taught by Kmiec et al. Therefore, the single oligonucleobase compound (polymer) taught by Kmiec et al does not anticipate claims 221-223, 232-236, 239, 241-245 and 247-248, all of which encompass an oligoribonucleotide that comprises two separate RNA strands.

With respect to instant claims 224-225, and 237-238, which recite linked strands, Applicant reiterates Kmiec et al.'s disclosure: "In the embodiments wherein the strands are complementary to each other at every nucleobase, the sequence of the first and second strands consists of at least two regions that are homologous to the target gene and one or more regions (the 'mutator regions') that differ from the target gene and introduce the genetic change into the target gene." (column 8, lines 26-34, emphasis added).

Applicant also notes that the Kmiec et al Patent, entitled "Eukaryotic Use of Improved Chimeric Mutational Vectors", discloses that the recombinagenic oligonucleobases are designed for chimeroplasty and are designed to introduce mutations into target DNA. Applicant also notes that by containing mutator regions, the recombinagenic oligonucleobases of Kmiec et al. cannot be fully complementary to the transcript of the target gene. As amended, claims 224-225, and 237-238, which encompass dsRNA strands which are linked, require that the dsRNA is "fully complementary" to an RNA transcript of a mammalian target gene.

Claims 224-225 and 237-238 also now require that the oligoribonucleotide inhibit the expression of a mammalian gene target. The DMV exemplified by Kmiec et al. confers a nucleotide mutation in the non-mammalian kanamycin resistance gene in bacteria. Since the DMV is complementary in part to a non-mammalian target DNA, the DMV is structurally distinct from the oligoribonucleotide encompassed by claims 224-225, and 237-238, which is fully complementary to an RNA transcript of a mammalian gene.

Claims 224-225 and 237-238 also now require the functional limitation that the dsRNA specifically inhibits the expression of the mammalian target gene. Kmiec et al. does not demonstrate that said DMV with its interrupted regions of complementarity, specifically inhibits the expression of the mammalian target gene. Therefore, the single oligonucleobase compound (polymer) DMV which contains mutator regions which are taught by Kmiec et al. to modify a gene, is structurally and functionally distinct from the dsRNA structure recited in claims 224-225, and 237-238, because the instantly recited dsRNA is fully complementary to an RNA transcript of a mammalian target gene. Because of this structural difference, the recombinagenic oligonucleobase taught by Kmiec et al. is not identical to the oligoribonucleotide of claims 224-225, and 237-238.

In view of the above listed differences between the DMV disclosed by Kmiec et al. and the oligoribonucleotides of the instant invention, Applicant submits that the referenced art of Kmiec et al. does not anticipate the claimed invention. Therefore, reconsideration and withdrawal of this rejection is respectfully requested.

Claim Rejections 35 U.S.C. § 103

Applicant gratefully acknowledged the withdrawal of the 103(a) rejection of claims 221, 232, 239 and 245 as being obvious Fire et al. (U.S. Patent No. 6,506,559) in view of Pasloske et al. (U.S. Patent 5,939,262).

Applicant also gratefully acknowledged the withdrawal of the 103(a) rejection of claims 221, 224, 225, 232, 237 and 238 as being obvious Fire et al. (U.S. Patent No. 6,506,559) in view of Jaschke et al (Nucleosides & Nucleotides, Vol. 15, pages 1519-1529, 1996)

Applicants submit that in view of the foregoing remarks, all issues relevant to patentability raised in the Office Action have been addressed. Applicants respectfully request the withdrawal of rejections over the claims of the present invention.

Respectfully submitted,

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